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PAUL T CLARK
CLARK & ELBING
176 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
PORTNER, VIRGINIA ALLEN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/423,042	Applicant(s) Guy et al
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 30, 2001 and Declaration September 17, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *5-12, 14-18, 25, and 37-46* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5-12, 14-18, 25, and 37-46* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-4 and 13 have been canceled.

Claims 5-12, 14-18 and 25 have been amended.

Claims 5-12, 14-18, 25 and 37-46 (new claims) are pending and under consideration.

Newly submitted claims 26-35 have been renumbered under 37 CFR1.126 to be claims 37-46, respectively.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Withdrawn

2. The disclosure objected to because of informalities in light of the amendment submitted removing the brackets [ ] at page 20, lines 25-27; page 21, lines 1-2 and 25-27; page 22, lines 4-8 in the specification.

3. Claims 11-12, and 43-44 rejected under 35 U.S.C. 112, first paragraph (scope of enablement), as previously applied to claim 25, has been obviated in so far as the claims recite Helicobacter pylori urease (UreB or UreA, a vaccinal vector comprising a sequence that encodes UreB or UreA) which have been shown and known to be therapeutic and prophilactic Helicobacter pylori antigens.

4. Claims 1, 2-4 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the claims having been canceled.

5. Claim 25 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the claim having been amended to clarify the agent and the methods steps.

6. Claims 6, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the claims having been amended to define a specific type of immune response that is Th-1 type.

7. Claims 5-12, 14-18 and 19 rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a

process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101 in light of the amendment of claims to recite a methods step and cancellation of some of the claims.

8. Claims 1-19 are rejected under 35 U.S.C. 102(e) as being anticipated by **Morrow et al** (US Pat 5,817,512) in light of Novak (1999), in light of the cancellation of some claims and amendment of all other claims to be directed to methods rather than compositions with a recited intended use.

9. Claims 1-19 are rejected under 35 U.S.C. 102(e) as being anticipated by **Holmgren** et al (US Pat 6,153,203), in light of the cancellation of some claims and amendment of all other claims to be directed to methods rather than compositions with a recited intended use.

10. Claims 1-19 rejected under 35 U.S.C. 102(e) as being anticipated by **Marciani** (US Pat 6,080,725), in light of the cancellation of some claims and amendment of all other claims to be directed to methods rather than compositions with a recited intended use.

11. Claims 1-19 rejected under 35 U.S.C. 102(b) as being anticipated by **Mohammadi et al** (The Journal of Immunology, Vol. 156, pages 4729-2738, 1996, reference of record), in light of the cancellation of some claims and amendment of all other claims to be directed to methods rather than compositions with a recited intended use.

12. Claims 1-19 are rejected under 35 U.S.C. 102(b) as being anticipated by **Pappo et al** (Infection Immunity, April 1995), in light of the cancellation of some claims and amendment of all other claims to be directed to methods rather than compositions with a recited intended use.

13. Claims 1-19 are rejected under 35 U.S.C. 102(b) as being anticipated by **Telford et al** (Drugs, 1996), in light of the cancellation of some claims and amendment of all other claims to be directed to methods rather than compositions with a recited intended use.

14. Claims 1-19 are rejected under 35 U.S.C. 102(b) as being anticipated by **Guy et al** (WO96/31235 in light of Guy et al (US Pat. 6,126,938 (English translation of WO96/31235), in light of the cancellation of some claims and amendment of all other claims to be directed to methods rather than compositions with a recited intended use.

15. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guy et al (WO96/31235) in light of Guy et al (US Pat. 6,126,938 (English translation of WO96/31235), in light of the claim having been amended and the rejection being reformatted below under 35 U.S.C. 102 (b).

Rejections Maintained

16. Claims 5-10, 14-18, 25 and 37-42, 45-46 are rejected under 35 U.S.C. 112, first paragraph (**scope**), as previously applied to claim 25 because the specification, while being enabling for induction of an immune response, does not reasonably provide enablement for the

administration of (Claim limitations recited in claim 10 and 42, and are encompassed by the base claims 5 and 25 from which claims 10 and 42 depend) any peptide or polypeptide or any DNA molecule or vaccinal vector that encodes any sequence for any peptide or polypeptide of Helicobacter pylori in a method of preventing or treating Helicobacter infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for reasons of record in paper number 7, paragraph 6.

17. Claims 7-9 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record in paper number 7, paragraph number 8.

Response to Amendment

18. The Declaration of Cynthia K. Lee, Ph.D. under 37 CFR 1.132 filed September 19, 2001 is insufficient to overcome the rejection of Claims 5-10, 14-18, 25 and 37-42, 45-46 rejected under 35 U.S.C. 112, first paragraph, as previously applied to claim 25, based upon the scope of enablement rejection as set forth in the last Office action because: while the independent claims 5 and 25 have now been amended to recite the phrase "prophylactically or therapeutically effective Helicobacter pylori antigen" and the data presented by Dr. Lee, shows a number of antigens that are effective in the induction of a prophylactic immune response, the instantly claimed invention is not limited to only the prophylactic immunization of a mammal, but also includes the therapeutic

immunization of a mammal with pre-existing chronic disease. The Declaration does not provide evidence of enablement for the full scope of the instantly claimed invention.

It is also the position of the examiner that the antigens used in the experiments presented in the Declaration of dated September 17, 2001, were protein antigens and not DNA, DNA vectors, or vaccinal vectors that encode peptide or polypeptide fragments of Helicobacter pylori antigens. Clearly the data provides evidence for the specific antigens set forth in the Declaration, but the scope of the claimed invention is not so limited to those embodiments exemplified in Dr. Lee's declaration or antigens known in the art at the time of filing which are able to induce a protective immune response. The data presented is not commensurate in scope with instantly claimed invention, as newly amended or newly submitted claims. The scope of enablement rejection is maintained for reasons of record in paper number 7, paragraph 6.

Response to Arguments

19. The rejection of claims 5-10, 14-18, 25 and 37-42, 45-46 under 35 U.S.C. 112, first paragraph (**scope**), as previously applied to claim 25, is traversed on the grounds that the claims are not limited to the administration of Helicobacter pylori antigens, that are prophylactically or therapeutically effective, the amount administered is an effective amount of antigen and the amount of experimentation need to determine whether an antigen is a protective antigen is not undue.

20. It is the position of the examiner that in light of the amendment of the claims, and through the submission of Declarative evidence, the scope of enablement rejection has been partially obviated,

but the Declarative evidence is not commensurate in scope with the instantly claimed invention which now includes Helicobacter antigen compositions defined to be, in claims 10 and 42, a peptide or polypeptide from Helicobacter pylori, a DNA molecule comprising a sequence encoding a peptide or polypeptide from Helicobacter pylori and a vaccinal vector comprising a sequence encoding a peptide or polypeptide of Helicobacter place under the control of elements for expression.

The full scope of the instantly claimed peptides and polypeptides that are fragments of Helicobacter proteins have not been described in the prior art to evidence the functional limitation of being an effective Helicobacter pylori antigen for induction of a prophilactic or therapeutic immune response. Helicobacter pylori urease fragment has been shown by Davin et al to induce a protective immune response, wherein the fragment has a specific size and sequence, but a single species of fragment known in the art to induce a prophylactic immune response when administered with an adjuvant does not provide enablement for the instantly claimed genus of methods directed to the utilization of any other peptide or polypeptide that does not evidence original descriptive support in the instant specification and having the now claimed therapeutic capability, the sequence and nature of the peptide or polypeptide not being known in the art as an effective Helicobacter pylori antigen.

Claims 10 and 42 also are directed to DNA molecule that encode peptides or polypeptides of Helicobacter pylori placed under the control of elements for its expression and vaccinal vectors that comprise the DNA molecules. The elements are not defined to be elements that would

function in a eukaryotic cell, the cell type present in all mammals. The elements are claimed to be any elements for expression.

Even if the claims were amended to recite elements for the expression in eukaryotic cells, what the sequences of DNA that encode Helicobacter pylori peptides and polypeptides that would induce a protective immune response over and enable the scope of the instantly claimed invention has not been described. The effective filing date for the Instant Specification is April 1997 and the publication of the Helicobacter pylori genome sequences was made available in August of 1997 (Nature, Tomb et al).

The full genome of sequences for Helicobacter pylori DNA was not known at the time of filing of the instant specification. Even if the claims were limited to DNA sequences known in the art, no specific DNA sequences other that the sequence for Helicobacter pylori urease were known to induce a protective immune response in a mammal. A single species of invention does not enable the full scope of the claims.

Roy (US Pat. 5,667,782, reference being made of record herein) shows a vaccinal vector that encodes Helicobacter pylori urease subunit A and B, wherein the expression of the UreB subunit was highly unstable (see col. 16, lines 21-24) and the UreA subunit expression was very good. The subunits immunoreacted with antibodies directed thereto, but the level of expression of UreB was modest (see col. 16, line 24), The UreB subunit in association with a polyhedrin promoter in a baculovirus vaccinal vector did not function to produce a high level of UreB, but produced a low level of expression of a UreB subunit that was unstable (see Roy et al, col.16,

lines 12-24) . Administration of an unstable vaccinal vector would not be expected to predictably function to induce a protective immune response. A critical combination of elements would be essential to the production and induce a protective immune response to a Helicobacter pylori antigen encoded by a DNA sequence for a peptide or polypeptide.

The scope of enablement rejection is maintained for reasons of record in paper number 7, paragraph 6.

21. The rejection of claims 7-9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is traversed on the basis that the claims set forth the predominant immune response induced to be a Th2 immune response and states that the recited ratios are the ratios that define a useful immune response and claims 7-9 are consistent with the base claim 6.

22. It is the position of the examiner the claim 6 defines the type of immune response to be a Th1 immune response and claims 7-9 define the type of immune response to be the combination of Th1 and Th2.

Claims 7-9 should depend from claim 5 not claim 6 that only provides for a single type of immune response to be stimulated.

If claim 6 is intended to define the induction of two types of immune response, it should be claimed as such, but claim 6 only defines the method to induce a single type of immune response to be induced.

Claims 7-9 define a method in which two different types of immune responses are induced. The predominant immune response induced is a Th2 rather than a Th1 type immune response. Claims 7-9 define primarily a Th2 immune response being induced and depends from claim 6 that sets forth the critical component of the immune response induced to be a Th1 immune response.

Applicant can claim any type of immune response for which the specification provides support, but to clarity of the claims is not only based up written description but the presence of clarity or the lack thereof. As Th2 and Th1 immune responses clearly are different, as they are induced by different reagents, and produce different effects in a mammal, having claims 7-9 depend from claim 6 is clearly confusing in light of claims 7-9 setting forth limitations that do not define the immune response to be only a Th1 immune response, or even to define the predominant immune response induced to be a Th1 immune response, as set forth in claim 6.

Claims 7-9 are still unclear for reasons of record in paper number 7, paragraph 8, and arguments set forth above.

New Claims/New Claim Limitations/New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 112

23. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. Claims 5 (independent claim), 10, 25 (independent claim) and 42 (submitted as claim 31 but renumbered under 37 CFR 1.126) are rejected under 35 U.S.C. 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 10 and 42, depend from claims 5 and 25 respectively and recite claim limitations directed to "a DNA molecule comprising a sequence encoding a peptide or polypeptide from Helicobacter pylori placed under the control of the elements necessary for its expression and a vaccinal vector comprising a sequence encoding a peptide or a polypeptide from Helicobacter pylori" and depend from independent claims directed to methods of inducing a protective immune response. In light of the fact that the instant specification does not disclose or provide original descriptive support for the now claimed genus of coding sequences for peptides or polypeptides of any specific size and sequence, and which DNA molecules must induce a protective immune response in any mammal, the instant specification does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed DNA molecules used in the newly submitted methods must function to induce a protective immune response. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does

not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

25. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

26. Claims 5-6, 16-17, 34, 37-38, 42 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the term "effective". What is the amount effective for?

Claims 5 and 6 have been amended to recite the phrase "by the subdiaphragmatic, systemic route." While the instant specification defines at page 7, first line, the phrase subdiaphragmatic to be that part of the mammal below the diaphragm, the term "systemic" is defined to encompass not only the parenteral route of administering a composition (instant specification, page 15, lines 2-8), but also mucosal routes of administering a composition (see page 19, last paragraph). Locations for both parenteral and mucosal administration are defined which are below the diaphragm, but are also taught to include nasal, ocular, pulmonary and intravenous all of which are systemic modes of administering an immune response, but are not

subdiaphragmatic. The recitation of these two different words that define two different processes, the first being subdiaphragmatic which would localize the immune response to those areas that are below the diaphragm and the second being a mode of administration that would induce an immune response that would be distributed throughout the entire body, would include administration to areas that are above the diaphragm.

Stedman's Medical Dictionary 27th Edition defines "local" immunity as: Having reference or confined to a limited part; not general or systemic and defines " systemic as: Relating to a system; specifically somatic, relating to the entire organism as distinguished from any of its individual parts. The term "subdiaphragmatic" defines a specific part, but "systemic" is not limited to any specific part of the mammal but to the entire organism. The presence of a ", (comma)" between the two words [subdiaphragmatic, systemic] helps to introduce confusion into the claim, as the two types of immune response contradict each other. The instant specification (see page 16, lines 9-20) provides an example of administering a composition to the dorsolumbar by the subcutaneous route, but the phrase "subdiaphragmatic, systemic" sets forth two different modes of administration and is much broader in scope than that which is defined at page 16, of the instant specification. The modes of administration encompassed by the scope of the claims that are systemic would not be limited to regions that are subdiaphragmatic. What modes of administration are intended by the words recited? Clarification is requested.

Claim 16 depends from claim 5 and recites the phrase "antigen is administered by a mucosal route followed by a parenteral route", wherein claim 5 recites the phrase "antigen by the

subdiaphragmatic, systemic route". While claim 5 recites "open" language which permits additional steps and utilization of additional antigens, claim 5 specifically defines the route of administration to be subdiaphragmatic or systemic routes and claim 16 does not set forth that the mucosal route is below the diaphragm, thus broadening the scope of claim 5. Claim 16 is not further limiting of claim 5 from which it depends. Is the parenteral route a subdiaphragmatic route? Is the mucosal route a local non-systemic mode of administering the antigen? Is the mucosal route below the diaphragm of the animal? The invention of claim 16 is not distinctly claimed based upon the combination of claim limitations set forth in claim 5 and 16.

Claim 17 depends from claim 16 and recites the phrase "is administered by a parenteral route, followed by a mucosal route, followed by a parenteral route followed by a mucosal route". Claim 16 requires the methods step to be carried out and to be "administered by a mucosal route followed by a parenteral route". Since claim 17 depends from claim 16 that defines a specific order for the composition to be administered and claim 17 defines an order totally different from that defined by claim 16, claim 17 is not further limiting of claim 16 from which it depends. Claim 17 recites methods steps that are just the opposite of those recited in claim 16. Claim 17 introduces confusion into the claimed method in view of the methods steps of claim 16 and 17 are not in agreement with each other, specifically the order the steps must be carried out. What steps follow each other in light of the fact that the steps are not consecutive or sequential? Clarification is requested.

Claim 34 recites the phrase "in which a", a conditional phrase in the passive voice "is co-administered". This methods step could be made clear through amending the claim to recite -- further comprising-- and deleting the phrase "in which"

Claim 37 depends from claim 25 which recites the phrase "in order the steps of", and recites the phrase "in which more than one mucosal administration is carried out". What is the order of the plurality of mucosal administrations? Does the additional mucosal administration come before or after the parenteral administration of antigen? Claim 37 does not define what order the additional step is carried out, thus not defining an order and broadening the scope of claim 25 from which it depends. Clarification is requested.

Claim 38 depends from claim 25 which recites the phrase "in order the steps of", and recites the phrase "in which more than one parenteral administration is carried out". What is the order of the plurality of parenteral administrations? Does the additional parenteral administration come before or after the mucosal administration of antigen? Claim 37 does not define what order the additional step is carried out, thus not defining an order and broadening the scope of claim 25 from which it depends. Clarification is requested.

Claim 42 recites the phrase "under the control of the elements necessary for its expression". Where and how is the DNA expressed? Will it be expressed in a prokaryotic cell or a eukaryotic cell? If the molecule is administered to a mammal, what are the elements necessary for its expression? How big is the DNA molecule? What is the peptide or polypeptide sequence of the DNA molecule encodes? How big is the peptide? Is the encoded peptide immunogenic?

How can a non-immunogenic peptide of less than 10 amino acids be used to induce a protective immune response in a mammal? As no protective peptides of only a few amino acids are known for any Helicobacter antigens, what is the sequence of the encoded protective peptide? Are the elements recited in the claims, the ribose sugars that make up the DNA? Clarification of the "elements" and the sequences with the recited characteristics is requested.

Claim 44 depends from claim 42 and recites the phrase "the Helicobacter pylori antigen is a DNA molecule". The DNA molecule of claim 44 is not required to be under the control of elements necessary for its expression, and thus broadens the scope of claim 42 from which it depends. How antigenic is Helicobacter pylori DNA? How is any DNA of any portion of Helicobacter pylori able to induce a protective immune response?

27. The use of the trademarks "QS-21, DC-Chol and Bay" have been noted in this application, specifically claim 35. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Please Note: the examiner is reading the claims to include both parenteral and mucosal administration of the Helicobacter antigen, as all of the claims recite the word "systemic route", and administration of a composition by a mucosal route can induce a systemic immune response as measured in a blood/serum sample.

28. Claims 5, 10, 11, 14, 15, are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (1995, reference of record).

The claimed invention is directed to a method of inducing an immune response to an Helicobacter pylori antigen composition, wherein the composition is administered by a systemic route.

Lee et al disclose a method of inducing an immune response to an Helicobacter pylori antigen composition, wherein the composition is administered by a systemic route (subcutaneously, see Table 1, page 166) and stimulated both an IgA and IgG immune response. The reference anticipates the instantly claimed invention.

29. Claims 5, 10, 14, 15, are rejected under 35 U.S.C. 102(b) as being anticipated by Dr. Varga Laszlo et al (1992, reference of record; English translation).

The claimed invention is directed to a method of inducing an immune response to an Helicobacter pylori antigen composition, wherein the composition is administered by a systemic route.

Dr. Varga Laszlo et al disclose a method of inducing an immune response to an Helicobacter pylori antigen composition, wherein the composition was administered by a systemic route (subcutaneously, see page 5, paragraphs 1-2, subcutaneous administration of Helicobacter pylori antigen to a human). The reference anticipates the instantly claimed invention.

30. Claims 5-6, 10-12, 14-16, 18, 25,37, 39-44 are rejected under 35 U.S.C. 102(b) as being anticipated by WO96/31235 in light of US Pat. 6,126,938 (English translation of French PCT; referred to herein as '938).

The claimed invention is directed to a method of inducing a protective immune response to a Helicobacter pylori antigen administered by a subdiaphragmatic route, systemic routes, wherein the routes include both mucosal and parenteral routes of administration of Helicobacter pylori antigen, the antigen being a protein, peptide, polypeptide or DNA encoding the peptide or polypeptide, with or without an adjuvant.

(Instant claims 5-6, 7-9,10 and 18, 25, and claims 42-44, submitted as claims 31-33)

WO96/31235 discloses a method of inducing a protective immune response to a Helicobacter pylori antigen administered by a subdiaphragmatic route, wherein the subdiaphragmatic route is systemic administration of the antigen (see antigen is a protein or DNA in a vector; see '938:col. 7, lines 7-18) to the dorsolumbar region (see WO96/31235 page 10, lines 37-41 and page 11, lines 1-17; English translation '938, see col. 5, lines 8-32).

(Instant claims 11-12 and 14) The Helicobacter pylori (see plasmids in figures) urease, UreA or UreB antigens (see '938: col. 7, lines 30-34) are taught to be administered by the systemic route (see '938: col. 6, lines 52-57)).

(Instant claims 15 and 41, submitted as claim 30) The systemic route includes subdiaphragmatic, (see '938, col. 5, line 15 and col. 18, lines 47-52), intravenous, intramuscular, intradermal, subcutaneous injection (see '938:col. 5, lines 8-11), as well as urogenital administration ('938, claim 5).

(Instant claim 16, 25, and claims 39-40, submitted as claims 28-29) The reference discloses a method of inducing a mucosal immune response to H.pylori antigen (oral, nasal, urogenital or intra gastric: see '938, col. 5, lines 33-49; especially lines 41-49) followed by a systemic administration with the antigen as a booster (see'938, col. 7, lines 35-50).

(Instant claim 37, submitted as claim 26)The reference also discloses the administration of H.pylori antigen to a mucosal surface one or more times (see '938, col. 9, lines 25-27;see Figures 9 and 10, and '938, col. 9, lines 44-46).

(Instant claim 46, formerly submitted as claim 35) Guy et al (WO96/31235) disclose the combination of H.pylori antigen together with a parenteral adjuvant, wherein the adjuvant may include alum, liposomes or viral particles(see '938, col. 5, lines 20-26). Among the specific liposomes disclosed are those made of DC-Chol (see col. 9, line 46).

By all comparable data, the host mammal, the composition: Helicobacter pylori antigen, and mode of administration of the composition are the same or equivalent to that of the instantly claimed invention. Guy et al WO'96 in light of '938 anticipates the instantly claimed invention.

Claim Rejections - 35 U.S.C. § 103

31. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

32. Claims 5, 17, 25 38 and 45 rejected under 35 U.S.C. 103(a) as being unpatentable over Guy et al (WO96', in light of '938) in view of Thomas, Jr. et al (US Pat. 5,919,463).

The claimed invention is directed to a method of inducing an immune response in a mammal with an Helicobacter pylori antigen, wherein the administration comprises a plurality of administrations to include parenteral followed by mucosal, a plurality of parenteral administrations, and a mucosal adjuvant is used in combination with the antigen, specifically LT, CT adjuvants.

See discussion of Guy et al (WO96 in light of '938) immediately above. The reference teaches the importance of combining Helicobacter antigens with adjuvants to include "detoxified forms of bacterial toxins" and their subunits (see '938, col. 6, lines 29-32).

The reference shows the combination of Helicobacter pylori antigen with an adjuvant, but differs from the instantly claimed invention by failing to show the combination of H.pylori antigen together with Clostridium difficile adjuvant.

Thomas, Jr. et al show immunogenic compositions of Helicobacter pylori antigen together with Clostridium difficile toxin, or cholera toxin (CT) or cholera toxin subunit B (CTB) or toxoid or the combination of CT and CTB (see Table 2, col. 10, lines 27-48) in an analogous art for the purpose of showing compositions for the optimization of an immunization protocol and the induction of a protective immune response with Helicobacter pylori urease antigen combined with a mucosal adjuvant.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the adjuvant of Guy et al with the mucosal adjuvant of Thomas Jr., et al because Thomas Jr., et al teach Helicobacter pylori to be a mucosal pathogen and the utilization of Helicobacter pylori together with a mucosal adjuvant upon administration to a mammal induced an enhanced protective immune response (see Thomas Jr, et al, col. 10, lines 50-55).

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of inducing a protective immune response with Helicobacter pylori antigen when administered to a mammal together with a mucosal bacterial toxin adjuvant, because both Guy et al and Thomas Jr, et al teach the importance of obtaining an enhanced immune response through combining a Helicobacter pylori

antigen together with an adjuvant in order to obtain the desired protective immune response and Thomas Jr. et al shows that Clostridium difficile toxin A and B are able to induce an enhanced immune response directed against H.pylori antigen(see Table 2, col. 10). Guy.et al in view of Thomas Jr. et al obviate the instantly claimed invention.

33. Claims 5, 17, 25 38 and 45 rejected under 35 U.S.C. 103(a) as being unpatentable over Guy et al (WO96', in light of '938) in view of Lee (US Pat. 5,837,240).

The claimed invention is directed to a method of inducing an immune response in a mammal with an Helicobacter pylori antigen, wherein the administration comprises a mucosal adjuvant is used in combination with the antigen, specifically clostridium toxin.

See discussion of Guy et al immediately above. The reference teaches the importance of optimizing immunization protocols using Helicobacter pylori antigen(see '938, col. 5, lines 53-57), wherein the immunization protocol combines several routes of administration (see '938, col. 3, lines 64-67) and teaches the combination of antigens with adjuvants to include "detoxified forms of bacterial toxins" and their subunits (see col. 6, lines 29-32).

The reference shows the combination of Helicobacter pylori antigen with an adjuvant, and teaches the administration of Helicobacter pylori antigen by the parenteral route but differs from the instantly claimed invention by failing to show the combination of H.pylori antigen together with LT or CT adjuvants, and the administration of H.pylori antigen to the parenteral route more than once.

Lee et al show immunogenic compositions of Helicobacter pylori antigen together with CT (see Lee et al, col. 12, lines 34-36 and Table 1, col. 13; col. 2, lines 49-55) or LT (see col. 17, lines 3-5, figure 9; Tables 6), and administration of H.pylori antigen by the parenteral route more than once (see col. 12, lines 41-47) in an analogous art for the purpose of showing compositions and routes of administration for the optimization of an immunization protocol and the induction of a protective immune response with Helicobacter pylori urease antigen.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the adjuvant of Guy et al with the mucosal adjuvant of Lee et al because Lee et al teach Helicobacter pylori to be a mucosal pathogen and the utilization of Helicobacter pylori antigen together with a mucosal adjuvant upon administration to a mammal induced an enhanced protective immune response.

It also would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Guy et al to comprise more than one parenteral administration of Helicobacter pylori antigen to a mammal in a method of inducing a protective immune response because Lee et al shows that through administering Helicobacter pylori antigen together with an adjuvant by the parenteral route (subcutaneous) four times resulted in the induction of a protective immune response that was confirmed through challenge of the mammal with Helicobacter felis (see Lee et al, col. 12, lines 47-52) in an art accepted mouse model.

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of inducing a protective

immune response with Helicobacter pylori antigen when administered to a mammal using more than one parenteral administration, when administered to a mammal together with a mucosal bacterial toxin adjuvant, or administered to a mammal using both parenteral and mucosal routes to prime and boost the immune response because both Guy et al and Lee et al teach the importance of optimizing the immune response induced is achieved through the route of administration of the antigen, (see Lee et al col. 12, lines 29-30 and Guy et al '938, col. 3, lines 64-67), the adjuvant selected to be combined with the Helicobacter pylori antigen, and the number of times the Helicobacter pylori antigen is administered to the mammal in order to obtain the desired protective immune response and Lee et al teaches through administration of Helicobacter pylori antigen by the parenteral route the desired protective immune response can be achieved, and also teach that through combining Helicobacter pylori antigens with bacterial toxins such as CT and LT, an enhanced mucosal immune response can be stimulated. Guy et al in view of Lee et al obviate the instantly claimed invention.

Conclusion

34. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

35. Kaplan (December 1993) is cited to show the vaccination of a human patient with Helicobacter pylori antigen by the subcutaneous parenteral route using multiple doses (prime and boosters, see page 923, col. 1).

36. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
August 23, 2002

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600